Mixed Hydroxypyridinonate Ligands as Iron Chelators[1]

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Received March 3, 2000

New ligands based on hydroxypyridinonate (HOPO) and other bidentate ligands are explored as iron(III) sequestering agents. These are based on the *N*,*N*′,*N*″-tris[(3-hydroxy-1-methyl-2-oxo-1,2-didehydropyrid-4-yl)-carboxamidoethyl]amine (TREN-Me-3,2-HOPO) platform in which one Me-3,2-HOPO ligand group is substituted with either a 2-hydroxyisophthalamide (TREN-Me-3,2-HOPOIAM) or a 2,3-dihydroxyterephthalamide (TREN-Me-3,2-HOPOTAM) moiety. The ferric complexes have been prepared and structurally characterized by X-ray diffraction: Fe[TREN-Me-3,2-HOPOIAM] crystallizes in the monoclinic space group *C*2/*c* with cell parameters $a = 18.1186(3)$ Å, $b = 17.5926(2)$ Å, $c = 25.0476(2)$ Å, $\beta = 98.142(1)°$, $Z = 8$. Fe[TREN-Me-3,2-HOPOTAM]$^-$ crystallizes in the monoclinic space group *C*2/*c* with cell parameters $a = 31.7556(12)$ Å, $b = 14.0087(6)$ Å, $c = 22.1557(9)$ Å, $\beta = 127.919(1)°$, $Z = 8$. The aqueous coordination chemistry of these ligands with both the ferric and ferrous redox states of iron has been examined using spectroscopic and electrochemical methods, giving log formation constants of 26.89(3) (β_{110}), 31.16(6) (β_{111}) for the ferric TREN-Me-3,2-HOPOIAM complexes and 33.89(2) (β_{110}), 38.45(2) (β_{111}) for the ferric TREN-Me-3,2-HOPOTAM complexes. For the reduced (ferrous) complexes values of 10.03(9) (β_{110}) and 13.7(2) (β_{110}) were observed for the Fe[TREN-Me-3,2-HOPOIAM]$^-$ and Fe[TREN-Me-3,2-HOPOTAM]$^{2-}$ complexes, respectively. These data provide a complete description of metal−ligand speciation as a function of pH and of redox activity. The ligands described in this work are part of a new class of heteropodate ligands which exploit the various chelating properties of several binding units within a single tripodal ligand and allow for systematic variation of the properties for medical or other applications.

Introduction

The ligand TREN-Me-3,2-HOPO (*N*,*N*′,*N*″-tris[(3-hydroxy-1-methyl-2-oxo-1,2-didehydropyrid-4-yl)carboxamidoethyl]-amine) is a versatile chelator, binding an array of metal ions with high affinity.[1−3] Recent studies have demonstrated the utility of ligands of this type as decorporation agents for the medical treatment of iron overload. Oral activity of TREN-Me-3,2-HOPO has been demonstrated in a rat model. This study also demonstrated that the hexacoordinate nature of this drug leads to greater efficacy when compared to a bidentate analogue.[4] As a class of ligands hydroxypyridinones (HOPOs) are known to exhibit excellent kinetics for iron removal from the serum protein transferrin; this has recently been demonstrated for a selection of multidentate HOPO-based ligands, including TREN-Me-3,2-HOPO.[5]

A disadvantage of TREN-Me-3,2-HOPO is that its metal(III) complexes generally suffer from poor water solubility. We have developed heteropodate analogues of TREN-Me-3,2-HOPO with substitution of one HOPO chelator unit for functional groups which are more easily derivatized. In this way the properties of the parent compound are varied by the inclusion of alternative functional groups, yielding new ligands with different chelation strength, redox properties, and/or solubility. The alternative functional groups which have been used are 2-hydroxyisophthalamide (IAM), 2,3-dihydroxyterephthalamide (TAM), salicylamide, and amino-bis(acetate). This group of ligands has been examined with respect to the NMR relaxation properties of their Gd(III) complexes.[6] In this paper we present the structural characterization and solution thermodynamic properties of the iron complexes of two of the heteropodand ligands (TREN-Me-3,2-HOPOIAM and TREN-Me-3,2-HOPOTAM) which are potential therapeutic agents for ferric ion sequestration.

Experimental Section

Synthesis. General. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Tris(2-aminoethyl)amine was distilled under vacuum from CaH_2. Flash silica gel chromatography was performed using Merck silica gel 40−70 mesh. Microanalyses were performed by the Microanalytical Services Laboratory, College of Chemistry, University of California, Berkeley. Mass spectra were recorded at the Mass Spectrometry Laboratory, College of Chemistry, University of California, Berkeley. All NMR spectra were recorded on either an AMX 300 or 400 Bruker superconducting Fourier transform spectrometer or a DRX 500 Brucker superconducting Digital spectrometer. Infrared spectra were measured using a Nicolet Magna IR 550 Fourier transform spectrometer. The 3-benzoxy-4-(2-thioxothazolidin-1-yl)carbonyl-2-pyridinone,[2] 1,4-bis-(2-thioxothiazolidin-1-yl)carbonyl-2,3-dimethoxybenzene,[7] and 1,3-bis-(2-thioxothiazolidin-1-yl)carbonyl-2-methoxybenzene[8] were prepared as previously described.

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10.1021/ic000239g CCC: $19.00
Published on Web 08/30/2000

Bis(Me-3,2-HOPO)TREN (1). Tris(2-aminoethyl)amine (TREN) (3.0 mmol) was dissolved in 150 mL of dry CH_2Cl_2. A solution of 3-benzoxy-4-(2-thioxothiazolidin-1-yl)carbonyl-2-pyridinone (6.0 mmol) in 100 mL of dry CH_2Cl_2 was added dropwise from a pressure-equalizing addition funnel. When the addition was finished, the reaction mixture was evaporated to dryness to give an amber oil. The oil was purified by silica column chromatography with 3−25% MeOH/CH_2Cl_2 as elutant. Evaporation of the solvent gave an amber oil. Yield: 62%. IR (film from CH_2Cl_2): ν 1600, 1646, 3375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 2.34 (t, J = 6.7 Hz, 6H, CH_2); 2.48 (t, J = 6.1 Hz, 2H, CH_2); 3.20 (q, J = 5.8 Hz, 4H, CH_2); 3.59 (s, 6H, CH_3); 5.32 (s, 4H, CH_2); 6.71 (d, 2H, J = 7.2 Hz, Ar*H*); 7.11 (d, 2H, J = 7.2 Hz, Ar*H*); 7.34 (m, 10H, Ar*H*); 7.97 (t br, 2H, N*H*). ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C): δ 37.6, 39.1, 50.3, 52.7, 56.2, 74.8, 104.7, 128.6, 128.7, 128.9, 131.0, 132.3, 136.2, 146.2, 159.6, 163.4.

Thiaz-TREN-Me-3,2-HOPOTAM (2). 1,4-Bis(2-thioxothiazolidin-1-yl)carbonyl-2,3-dimethoxybenzene (0.02 mol) was dissolved in 240 mL of dry CH_2Cl_2. **1** (2.0 mmol) dissolved in 60 mL of dry CH_2Cl_2 was added dropwise from a pressure-equalized addition funnel. When the addition was complete, the solution was evaporated to a volume of 100 mL and the mixture was purified by silica column chromatography. Elution with 0−5% MeOH/CH_2Cl_2 gave the product as a yellow foam after evaporation of solvent. Yield: 69%. IR (film from CH_2Cl_2): ν 1601, 1647, 2940 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 2.35 (t, J = 6.6 Hz, 4H, CH_2); 2.52 (t br, 2H, CH_2); 3.18 (q br, 4H, CH_2); 3.30 (q br, 2H, CH_2); 3.38 (t, J = 7.3 Hz, 2H, CH_2); 3.53 (s, 6H, NCH_3); 3.79 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 4.60 (t, J = 7.3 Hz, 2H, CH_2); 5.32 (s, 4H, CH_2); 6.62 (d, J = 7.1 Hz, 2H, Ar*H*); 7.05 (dd, 3H, Ar*H*); 7.30 (m, 10H, Ar*H*); 7.73 (d, J = 8.1 Hz, 1H, Ar*H*); 7.86 (m, 4H, N*H*). ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C): δ 29.2, 37.4, 37.6, 37.7, 52.5, 53.6, 55.4, 61.4, 74.8, 104.4, 123.3, 123.4, 128.6, 128.7, 128.8, 129.5, 129.6, 130.5, 132.3, 132.8, 136.4, 146.2, 150.1, 151.1, 159.4, 163.3, 164.4, 166.8, 201.1. Anal. Calcd (found) for $C_{47}H_{51}N_7O_{10}S_2$: C, 60.18 (59.85); H, 5.48 (5.58); N, 10.45 (10.46).

Protected TREN-Me-3,2-HOPOTAM (3). 2 (2.0 mmol) was dissolved in 20 mL of CH_2Cl_2; 5 mL of 40% (by weight) methylamine in water was added to the organic solution. The mixture was shaken until all the yellow color dissipated. The mixture was extracted with 30 mL of brine, 2 × 30 mL of 1.0 M KOH/saturated NaCl, and 40 mL of water. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness to give the product as a white foam. Yield: 83%. IR (film from CH_2Cl_2): ν 1538, 1645, 3384 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 2.36 (t, J = 6.6 Hz, 4H, CH_2); 2.54 (t, J = 5.9 Hz, 2H, CH_2); 3.01 (d, J = 4.8 Hz, 3H, NCH_3); 3.18 (q, J = 6.0 Hz, 4H, CH_2); 3.30 (q, J = 5.6 Hz, 2H, CH_2); 3.56 (s, 6H, NCH_3); 3.84 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 5.30 (s, 4H, CH_2); 6.61 (d, 2H, J = 7.2 Hz, Ar*H*); 7.05 (d, J = 7.2 Hz, 2H, Ar*H*); 7.30 (m, 10H, Ar*H*); 7.72 (q, J = 8.3, 15.6 Hz, 2H, Ar*H*); 7.86 (m, 4H, N*H*). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ 26.7, 37.4, 37.5, 37.7, 52.5, 61.6, 74.9, 104.6, 125.6, 125.8, 126.3, 128.7, 128.8, 129.0, 129.9, 130.5, 132.2, 136.4, 146.4, 151.3, 159.5, 163.4, 164.5), 165.2. Anal. Calcd (found) for $C_{45}H_{51}N_7O_{10}$: C, 63.59 (63.19); H, 6.05 (6.14); N, 11.54 (11.26). (+)-FABMS: m/z 850 [M^+ + H].

TREN-Me-3,2-HOPOTAM (4). 3 (1.0 mmol) was dissolved in 25 mL of dry CH_2Cl_2. The solution was frozen using liquid N_2, and BBr_3 (0.05 mol) was added via syringe. The reaction mixture was allowed to warm to room temperature, and the resulting yellow slurry was stirred for 48 h. The solvent was removed in vacuo and the resulting solid quenched with MeOH. The MeOH suspension was added to 75 mL of water and then boiled for 3 h. The reduced solution (∼40 mL) was hot filtered and then gradually cooled to 4 °C. A white powder precipitated from the aqueous solution and was collected by filtration and oven dried. Yield: 82%. IR (KBr pellet): ν 1332, 1652, 3364 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ 2.82 (d, J = 4.2 Hz, 3H, NCH_3), 3.46 (s br, 12H, CH_2), 3.70 (s br, 6H, NCH_3), 6.42 (d, 2H, J = 7.3 Hz, Ar*H*), 7.15 (d, J = 7.3 Hz, 2H, Ar*H*), 7.29 (q, J = 7.4, 8.7 Hz, 2H, Ar*H*), 8.62 (t br, 2H, N*H*), 8.91 (d br, 1H, N*H*), 8.97 (t br, 1H, N*H*). ^{13}C NMR (500 MHz, DMSO-d_6, 25 °C): δ 26.5, 34.3, 34.5, 37.3, 52.0, 103.2, 116.1, 116.6, 117.2, 117.4, 117.8, 128.1, 147.9, 150.1, 150.7, 158.5, 166.6, 169.5, 169.7. Anal. Calcd (found) for $C_{29}H_{36}N_7O_{10}Br_1 \cdot 2H_2O$: C, 45.92 (45.94); H, 5.31 (5.19); N, 12.93 (12.66). (+)-FABMS: m/z 642 [M^++H].

Fe[TREN-Me-3,2-HOPOTAM]$^-$. 4 (0.1 mmol) was dissolved in 10 mL of MeOH. $FeCl_3 \cdot 6H_2O$ (0.1 mmol) was added to the methanol solution followed by 4 equiv (per mole of ligand) of 0.1 N KOH in MeOH. The solution was heated to reflux for 2 h and then was evaporated to dryness. The residue was suspended in iPrOH, sonicated, and filtered. The complex was recrystallized from a DMF solution diffused with diethyl ether.

Thiaz-TREN-Me-3,2-HOPOIAM (5). 1,3-Bis(2-thioxothiazolidin-1-yl)carbonyl-2-methoxybenzene (0.02 mol) was dissolved in 240 mL of dry CH_2Cl_2. Dropwise, **1** (1.9 mmol) dissolved in 60 mL of dry CH_2Cl_2 was added from a pressure-equalized addition funnel. When the addition was complete, the solution was evaporated to a volume of 100 mL and purified by silica column chromatography. Elution with 0−5% MeOH/CH_2Cl_2 gave the product as a yellow foam after evaporation of solvent. Yield: 86%. IR (film from CH_2Cl_2): ν 1539, 1647, 2930 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 2.35 (t, J = 6.9 Hz, 4H, CH_2), 2.51 (t, J = 6.4 Hz, 2H, CH_2), 3.18 (q, J = 6.2 Hz, 4H, CH_2), 3.28 (q, J = 5.7 Hz, 2H, CH_2), 3.41 (t, J = 7.5 Hz, 2H, CH_2), 3.56 (s, 6H, NCH_3), 3.78 (s, 3H, OCH_3), 4.63 (t, J = 7.3 Hz, 2H, CH_2), 5.30 (s, 4H, CH_2), 6.64 (d, J = 7.2 Hz, 2H, Ar*H*), 7.07 (d, J = 7.2 Hz, 2H, Ar*H*), 7.19 (t, J = 7.7 Hz, 1H, Ar*H*), 7.32 (m, 11H, Ar*H*), 7.55 (br t, 1H, N*H*), 7.86 (br t, 2H, N*H*), 8.02 (d, J = 6.0 Hz, 1H, Ar*H*). ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C): δ 29.1, 37.4, 37.6, 37.7, 52.6, 52.7, 55.7, 63.1, 74.9, 104.7, 124.4, 127.3, 128.8, 128.9, 129.0, 129.1, 130.5, 132.2, 134.1, 136.4, 146.5, 155.6, 146.5, 159.5, 163.4, 164.9, 167.4, 201.3. Anal. Calcd (found) for $C_{46}H_{49}N_7O_9S_2 \cdot H_2O$: C, 59.64 (59.66); H, 5.73 (5.55); N, 10.47 (10.59).

Protected TREN-Me-3,2-HOPOIAM (6). 5 (1.6 mmol) was dissolved in 20 mL of CH_2Cl_2; 2 mL of 40% (by weight) methylamine in water was added to the organic solution. The mixture was shaken until all the yellow color dissipated. The mixture was extracted with 30 mL of brine, 2 × 30 mL of 1.0 M KOH/saturated NaCl, and 40 mL of water. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness to give the product as a white foam. Yield: 74%. IR (film from CH_2Cl_2): ν 1601, 1652, 2938 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 2.27 (br s, 4H, CH_2), 2.46 (br s, 2H, CH_2), 2.86 (d, J = 4.5 Hz, 3H, CH_3), 3.09 (br s, 4H, CH_2), 3.20 (br s, 2H, CH_2), 3.40 (s, 6H, NCH_3), 3.66 (s, 3H, OCH_3), 5.17 (s, 4H, CH_2), 6.39 (d, J = 7.1 Hz, 2H, Ar*H*), 6.93 (d, J = 7.2 Hz, 2H, Ar*H*), 7.02 (t, J = 8.4 Hz, 1H, Ar*H*), 7.15 (m, 11H, Ar*H*), 7.70 (br m, 3H, Ar*H*/N*H*). ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C): δ 26.7, 37.4, 37.6, 52.4, 63.3, 74.8, 104.5, 124.2, 128.2, 128.8, 130.4, 132.3, 133.0, 136.2, 146.1, 155.5, 159.3, 163.3, 165.2, 166.3. Anal. Calcd (found) for $C_{48}H_{50}N_6O_8$: C, 64.46 (64.28); H, 6.02 (6.33); N, 11.96 (11.61). (+)-FABMS: m/z 820 [M^++H].

TREN-Me-3,2-HOPOIAM (7). 6 (1.1 mmol) was dissolved in 25 mL of dry CH_2Cl_2. The solution was frozen using liquid N_2, and BBr_3 (0.05 mol) was added via syringe. The reaction mixture was allowed to warm to room temperature, and the resulting yellow slurry was stirred for 48 h. The reaction mixture was evaporated in vacuo and the resulting solid quenched with MeOH. The MeOH suspension was added to 75 mL of water, which was boiled for 3 h. The reduced solution (∼40 mL) was filtered while hot and then gradually cooled to 4 °C. A white powder precipitated from the aqueous solution and was collected by filtration and oven dried. Yield: 50%. IR (KBr pellet): ν 1541, 1598, 3376 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ 2.83 (d, J = 4.2 Hz, 3H, NCH_3), 3.46 (s br, 12H, CH_2), 3.70 (s br, 6H, NCH_3), 6.40 (d, J = 7.3 Hz, 2H, Ar*H*), 6.94 (t, J = 7.8 Hz, 1H, Ar*H*), 7.12 (d, J = 7.3 Hz, 2H, Ar*H*), 7.93 (d, J = 7.7, 2H, Ar*H*), 8.00 (d, J = 6.5, 1H, Ar*H*), 8.62 (t br, 2H, N*H*), 8.83 (t br, 1H, N*H*), 8.95 (d br, 1H, N*H*). ^{13}C NMR (500 MHz, DMSO-d_6, 25 °C): δ 26.5, 34.6, 37.2, 52.4, 52.6, 103.3, 116.8, 117.4, 118.5, 119.7, 128.0, 132.1, 134.4, 147.6, 158.5, 160.1, 166.4, 167.1, 169.2. Anal. Calcd (found) for $C_{29}H_{36}N_7O_9Br_1 \cdot 1.5MeOH \cdot 2H_2O$: C, 46.33 (46.15); H, 5.86 (5.46); N, 12.40 (12.14). (+)-FABMS: m/z 626 [M^+ + H].

Fe[TREN-Me-3,2-HOPOIAM]. 7 (0.1 mmol) was dissolved in 10 mL of MeOH. $FeCl_3 \cdot 6H_2O$ (0.1 mmol) was added to the methanol solution followed by an excess of pyridine. The solution was heated to reflux for 2 h and then was evaporated to dryness. The residue was purified by silica column chromatography. Elution with 0−15% MeOH/

Table 1. Crystal Data and Structure Refinement for Fe[TREN-Me-3,2-HOPOIAM] and Fe[TREN-Me-3,2-HOPOTAM]K

Compound	Fe[TREN-Me-3,2-HOPOIAM]	Fe[TREN-Me-3,2-HOPOTAM]K
fw	602.45	732.56
temp, K	170(2)	149(2)
cryst syst	monoclinic	monoclinic
space group	*C*2/*c*	*C*2/*c*
unit cell dimens		
a, Å	18.1186(3)	31.7556(12)
α, deg	90	90
b, Å	17.5926(2)	14.0087(6)
β, deg	98.142(1)	127.919(1)
c, Å	25.0476(2)	22.1557(9)
γ, deg	90	90
vol, Å^3; *Z*	7903.5(2); 8	7775.3(5); 8
density (calcd), g cm^{-3}	1.013	1.252
cryst size (mm)	0.30 × 0.30 × 0.10	0.20 × 0.10 × 0.05
abs correction, μ, mm^{-1}	0.419	0.551
reflns collected	16165	18143
indep reflns	5633 [*R*(int) = 0.0339]	6860 [*R*(int) = 0.0580]
data/restraints/params	5633/0/496	6852/0/579
goodness-of-fit on F^2 [a]	1.095	1.203
final *R* indices [$I > 2\sigma(I)$] [b]	R1 = 0.0540, wR2 = 0.1495	R1 = 0.0706, wR2 = 0.1259
R indices (all data) [b]	R1 = 0.0698, wR2 = 0.1644	R1 = 0.1068, wR2 = 0.1473
largest diff peak and hole, e·Å^{-3}	0.739 and −0.443	0.478 and −0.524

[a] GOF| = $[\sum w(|F_o| - |F_c|)^2/(N_o - N_v)]^{1/2}$, where $w = 1/(\sigma^2|F_o|)$. [b] R1 = $\sum||F_o| - |F_c||/\sum|F_o|$, wR2 = $(\sum[w(F_o^2 - F_c^2)^2]/\sum[wF_o^4])^{1/2}$. Radiation wavelength ($\lambda$) = 0.71073 Å

CH_2Cl_2 gave the product as a red solid after evaporation of solvent. The complex was recrystallized from an acetonitrile solution diffused with diethyl ether.

Structure Determination and Refinement. All X-ray structure data sets were collected, solved, and refined as previously described.[9−12] The crystallographic details of each structure are given in Table 1, including crystal parameters and refinement details. Crystals of Fe[TREN-Me-3,2-HOPOIAM] were grown as red blocks from a solution of the complex in acetonitrile diffused with diethyl ether. Two diethyl ether molecules (one ordered and one disordered) are in the asymmetric unit. Crystals of Fe[TREN-Me-3,2-HOPOTAM]$^-$ were grown as dark red blocks from a solution of the complex in DMF diffused with diethyl ether. A potassium counterion, one disordered DMF molecule, one methanol molecule, and three water molecules are in the asymmetric unit.

Electrochemistry. The potentiostat used was supplied by Bio-Analytical Systems (BAS, model 100a). All experiments used a three-electrode cell composed of the following electrodes: Pt wire auxiliary, saturated calomel reference (SCE, BAS part no. MF-2055), and Hg working (Princeton Applied Research (PAR) model 303a in hanging-mercury-drop-electrode (HMDE) mode, medium drop size). The SCE electrode was combined with the PAR 303a assembly by insertion via the sample-addition port. Drop knocking and solution purging by the PAR 303a was controlled remotely from the potentiostat; a fresh Hg drop was used for each scan.

The potential of the reference electrode was calibrated against $K_4[Fe(CN)_6]$ (Aldrich, trihydrate, 99%) using a Pt working electrode (BAS part no. MF-2013). Pt was used since $K_4[Fe(CN)_6]$ exhibits absorption behavior at Hg electrodes. At Pt a reversible couple consistent with diffusion from solution was observed by cyclic voltammetry (peak potentials constant to within ±2 mV over the range of scan rates 15−200 mV/s, peak current proportional to the square root of scan rate ($R^2 = 0.999$, $n = 9$), peak separation of 72 ± 3 mV). The standard potential for the $Fe(CN)_6^{3/4-}$ couple at 0.1 M ionic strength in aqueous KCl was determined to be +415 mV vs NHE from an interpolation of results presented in the literature,[13] and on the basis of this value the experimental potential of the SCE electrode used in this work was determined to be +239 ± 2 mV vs NHE, compared with the literature value of +241 mV vs NHE.[14]

Aqueous solutions of the ferric heteropodates were prepared at 5×10^{-5} M Fe, 1×10^{-4} M ligand and contained 0.01 M ammonium acetate as buffer with addition of KOH or HCl to give the desired pH. The ionic strength was set to 0.1 M by addition of KCl. These solutions were deoxygenated by stirred purging with Ar gas for 10 min prior to the acquisition of square wave voltammograms. For each scan the square wave modulation amplitude was 25 mV, the step potential was 2 mV, 16-point current sampling was selected, and the square wave frequency was varied over the range 5−50 Hz in order to test for reversibility of the system. Reversibility was evaluated by comparing the digitized current−potential response to the theoretical response as described in the literature for square wave voltammetry.[15] According to eq 1 a plot of the function Γ against potential, *E*, has an inverse slope of $2.3RT/nF$ ($59/n$ mV) and a horizontal intercept at $E = E°$. Terms are defined as follows: cosh is the hyperbolic cosine function, E_{SW} is the square wave modulation amplitude, ΔI is the square wave difference current, ΔI_p is the peak difference current, and the physical constants *n*, *F*, *R*, and *T* hold their usual meanings.

$$\Gamma = \log[z \pm (z^2 - 1)^{1/2}] = \frac{nF}{2.3RT}(E - E°) \qquad (1)$$

where ± = − for $E < E°$, ± = + for $E \geq E°$, and

$$z = \left(\frac{\Delta I_p}{\Delta I}\right)\left(1 + \cosh\left(\frac{nF}{RT}E_{SW}\right)\right) - \cosh\left(\frac{nF}{RT}E_{SW}\right)$$

Solution Thermodynamics: Preparation of Solutions. Base, acid, and electrolyte solutions were prepared as previously described[12] and were stored under argon gas in order to reduce the ingression of CO_2 from the atmosphere. A stock solution of iron was prepared by dissolution of $Fe(NO_3)_3$ (Aldrich, 99.99+%, nonahydrate) in the standard (~0.1 M) HCl solution prepared as above. This solution was standardized by titration against a stock solution of EDTA (disodium EDTA, biochemika grade, Fluka) using an adapted method.[16] For this an aliquot of the Fe^{3+} solution was taken with a calibrated glass-bulb pipet and diluted into 25 mL of 0.05 M ammonium acetate (ACS grade, Sigma) to give a pH of ~2.5. This solution was titrated with the standard EDTA solution. One drop of a 0.1% solution of Variamine Blue B (hydrochloride, 98%, Sigma) was added near the end to provide a visual indicator. The EDTA solution was standardized using a potentiometric titration from pH 5 to 9 and back to 5 with the standard acid/base solutions.

Titration Equipment. The titration cell was built in-house and composed of glass with a Teflon lid. The cell was held under a positive pressure of argon to eliminate the ingression of CO_2. A water jacket around the cell provided temperature control (25 ± 0.1 °C) by means of circulating water from a thermostatic bath (Neslab). For the collection of spectral data an opening was cut into the side of the cell. A quartz curvette was cut open and attached to the opening in the titration cell using silicone rubber glue (General Electric RTV 102). This entire apparatus, including a water-powered magnetic stirrer, was small enough to be housed within the bay of the spectrophotometer with the quartz curvette intercepting the light path.

(9) *SMART, Area-Detector Software Package*; Siemens Industrial Automation, Inc.: Madison, 1994.
(10) *SAINT, SAX Area-Detector Integration Program*, v. 4.024; Siemens Industrial Automation, Inc.: Madison, 1994.
(11) *SHELXTL, Crystal Structure Analysis Determination Package*; Siemens Industrial Automation, Inc.: Madison, 1994.
(12) Cohen, S. M.; Meyer, M.; Raymond, K. N. *J. Am. Chem. Soc.* **1998**, *120*, 6277.
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Fully automated instrumentation was used for titrant delivery and the collection of potentiometric and/or spectrophotometric data. Metrohm autoburets (Titrino 702 SM or Dosimat 665) were used for titrant delivery. Either an Accumet pH meter (model AR15 or 15) or the Metrohm Titrino were used for electrode potential measurement. A Hewlett-Packard 8452a spectrophotometer (diode array), controlled via a GPIB interface, was used for the collection of absorbance data. Instruments were operated using a PC running modules of the LABVIEW programming environment.[17] The modules were either written or obtained from National Instruments.[18,19]

Titrations. General Methods. A glass bulb electrode was used for the measurement of pH (Corning high performance, combination reference electrode, Cat. No. 476146). This was calibrated against $[H^+]$, i.e., proton *concentration* as opposed to *activity*, using a method previously described.[20] Calibration data was analyzed using the program GLEE[21] allowing refinement of the parameters $E°$, s, and γ. A fixed value of 13.78 was used for pK_w.[22,23]

Two complementary titration methods were used: "batch titrations" used a collection of ~15 samples prepared in glass flasks, each with a slight variation in pH; "incremental titrations" used a single solution placed within a titration cell and incrementally perturbed by addition of titrant. Measurements of pH and/or absorbance were collected for each addition after waiting for equilibration (90 s for protonation studies, 2 h for competition experiments), at which time potentiometric measurements were recorded at 6 s intervals. The mean value was recorded once 10 measurements had been obtained in which the standard deviation in the measured electrode potential was less than 0.05 mV. If this criterion was not reached within 10 min, then the point was omitted from the data set. Absorbance measurements were collected in the iron complexation experiments using a 10 s integration period. Spectra were recorded before and after collection of potentiometric data, and the whole measurement cycle was repeated until the absorbance measurements agreed to within 0.001 absorbance units. All absorbance measurements were less than 1.0 absorbance unit.

Protonation Constants. The protonation constants of the heteropodand ligands were determined in potentiometric experiments using an incremental titration method with an equilibration time of 90 s. For each ligand two experiments were performed, a forward titration against KOH and reverse titration against HCl, giving four titrations for each ligand. A known volume of electrolyte (0.1 M KCl) was combined with a weighed portion of ligand (giving a concentration of either 0.5 or 1.0×10^{-3} M). The resulting solutions were titrated from pH ~4 to 11 and then in reverse to pH 4. An average of 75 data points were collected in the course of each titration for a total of ~300 measurements per ligand. The results from each pair of titrations were combined for nonlinear least squares refinement (vide infra) giving the values and standard deviations for the protonation constants as listed in Table 2. The proton and ligand concentrations were treated as refined parameters, giving concentrations that were within 5% of the analytical values. The global σ values were between 1.4 and 4.7.

Formation Constants: Incremental Titrations. In the titration cell (in the following order) 100.0 mL of electrolyte solution was combined with aliquots of standardized EDTA and Fe^{3+} solutions and a weighed portion of ligand. The following concentrations were used: EDTA $2\times-4 \times 10^{-4}$ M, Fe^{3+} 5×10^{-5} M, ligand 1×10^{-4} M. Each experiment consisted of two titrations (forward and reverse titrations) with ~24 points collected over ~48 h (an equilibration time of 2 h was used for each point). Each data point consisted of a potentiometric measurement (pH) and an absorbance spectrum. The experiments were duplicated for each ligand giving four titrations for each metal−ligand system.

Table 2. Iron Formation Constants for the Heteropodand Ligands Given as log β Values as Defined in Eq 2[a]

		log β_{mlh}	
species	*mlh*	TREN-Me-3,2-HOPOIAM	TREN-Me-3,2-HOPOTAM
LH	0 1 1	8.28(2)	11.12(5)
LH_2	0 1 2	15.46(1)	19.25(1)
LH_3	0 1 3	21.47(1)	26.37(2)
LH_4	0 1 4	26.51(1)	32.25(1)
LH_5	0 1 5		37.35(1)
method B[b]			
FeL	1 1 0	26.51(3)	33.14(2)
FeLH	1 1 1	31.36(1)	38.39(1)
method I			
FeL	1 1 0	26.89(3)	33.89(2)
FeLH	1 1 1	31.16(6)	38.45(2)
pM[c]		26.7	30.2
$Fe^{II}L$[d]	1 1 0	10.03(9)	13.7(2)

[a] Values in parentheses give the estimated uncertainties in the least significant figure based on the variation between replicate experiments. [b] Titration method: B = batch, I = incremental. [c] pM is defined as the negative logarithm of free metal concentration at pH 7.4 and total concentrations of 1 μM iron and 10 μM ligand. [d] Ferrous iron formation constant determined electrochemically, error terms in parentheses are derived from the uncertainties in the reduction potentials and in the ferric formation constants.

Formation Constants: Batch Titrations. A single batch titration was performed for each Fe−heteropodand system. A stock solution was prepared (200.0 mL) containing 0.1 M KCl, EDTA (4×10^{-4} M for Fe[TREN-Me-3,2-HOPOTAM]$^-$, 2×10^{-4} M for Fe[TREN-Me-3,2-HOPOIAM]), 5×10^{-5} M Fe^{3+}, and 1×10^{-4} M ligand. The reagents were added in the order given to a volumetric flask that was filled to the mark with Millipore water and aliquots subsequently removed with an analytical grade pipet to generate each sample. Titers of between 0 and 0.06 mL of standardized ~0.1 M KOH solution were added to each sample (the amount required was established by speciation calculations using the program HYSS).[24,25] After the samples had been equilibrated in the dark at 25 °C for at least 100 h, a potentiometric measurement of pH and an absorbance spectrum were recorded for each solution.

Data Treatment and Refinement. The data from each titration were imported into the program HYPERQUAD and treated by nonlinear least squares refinement.[26,27] All equilibrium constants were defined as cumulative formation constants, β_{mlh} according to eq 2; the heteropodand ligands are designated as L. The stepwise ligand protonation constants, K^a_n, may be derived from these cumulative constants according to eq 3 (describes proton *association* constants). Competition methods, using EDTA as a competitor, were used for titrations involving metal−ligand coordination. The equilibration of iron between the ligand and competitor was calculated by including the proton association and iron formation constants for EDTA, and the ferric ion hydrolysis constants as fixed parameters in the HYPERQUAD refinements (the actual values used are tabulated in the Supporting Information).[28−30] Due to the hexacoordinate nature of the competing ligands it was assumed that ternary (i.e., EDTA−Fe−heteropodand) complexes were not formed. This assumption was supported by spectral data showing that the band

(17) *LABVIEW*, 5.0.1 ed.; National Instruments Corporation, http://www.ni/com/; 11500 N Mopac Expwy, Austin, TX 78759-3504.
(18) *Labview interface for Dosimat 665*: ftp://ftp.natinst.com/support/instr_drivers/labview/windows/current/library/serial/mmds665.zip.
(19) *Labview interface for HP8452a*: ftp://ftp.natinst.com/support/labview/instruments/windows/donated/previous/gpib/hp8452.zip.
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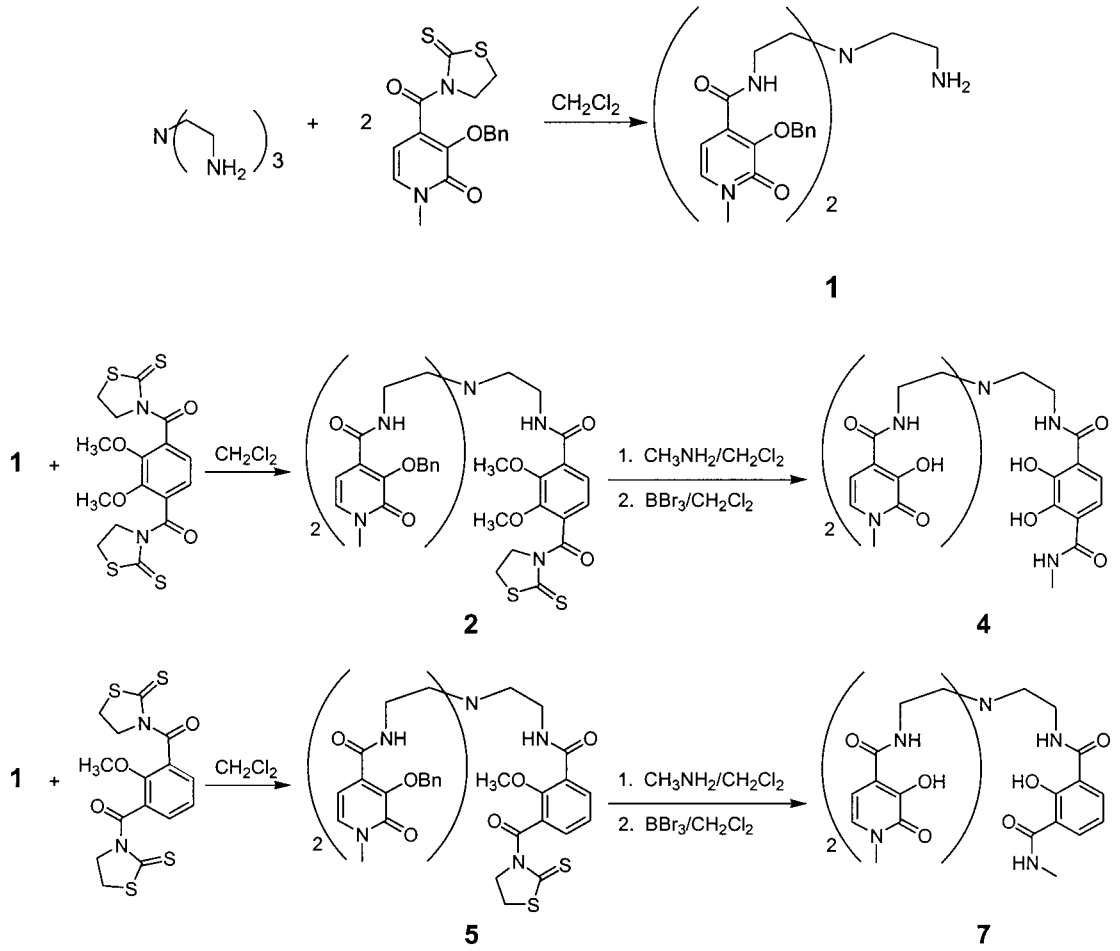
Scheme 1



shapes of the LMCT transitions of the iron−heteropodand complexes were unchanged in the presence and absence of EDTA. A typical analysis of a competition titration included ~20 equilibrium constants (K^a and Fe constants for the heteropodand ligand and for EDTA, Fe hydrolysis constants, and K_w). Despite this complexity the refinements were stable since only two constants were refined (the formation constants β_{110} and β_{111}). The ideal conditions for these experiments were established by prior modeling using the speciation program HYSS[24,25] and estimated values of the formation constants.

$$m\mathrm{Fe} + l\mathrm{L} + h\mathrm{H} \rightleftharpoons [\mathrm{Fe}_m\mathrm{L}_l\mathrm{H}_h]$$

$$\beta_{mlh} = \frac{[\mathrm{Fe}_m\mathrm{L}_l\mathrm{H}_h]}{[\mathrm{Fe}]^m[\mathrm{L}]^l[\mathrm{H}]^h} \quad (2)$$

$$K^a_n = \frac{[\mathrm{LH}_n]}{[\mathrm{H}][\mathrm{LH}_{n-1}]} = \frac{\beta_{01n}}{\beta_{01(n-1)}} \quad (3)$$

The program HYPERQUAD allows treatment of potentiometric and/or spectrophotometric data and the simultaneous treatment of multiple titration curves. An important consideration when treating data acquired from different measurement techniques (i.e., absorbance and potentiometric measurements) is the relative weighting of each observation in the refinements. For potentiometric observations the errors are assigned as 0.002 mL and 0.002 pH. For absorbance measurements the error terms were determined using a holmium oxide glass filter as directed by the program HYPERQUAD.[26,27]

For incremental titrations each pair of titrations (i.e., forward titration against KOH and reverse titration against HCl) were combined for simultaneous refinement. A selection of ~40 wavelengths within the range 410−650 nm were taken from the spectral data and incorporated into the refinements, giving an absorbance matrix of ~600 data points. Only the complexes FeL and FeLH have significant absorbance. The proton concentrations were refined, and all other concentrations were held at estimated values determined from the volume of standardized stock or the measured mass of ligand. The formation constants are given in Table 2. The global σ values for refinement varied between 1.3 and 1.9 for the 10 titrations (4 incremental titrations and a single batch titration for each ligand).

Results

The two ligands were synthesized according to the methods shown in Scheme 1. Two equivalents of 3-benzoxy-4-(2-thioxothiazolidin-1-yl)carbonyl-2-pyridinone[2] was slowly added to 1 equiv of TREN in CH_2Cl_2. Purification by silica gel flash chromatography provided the disubstituted TREN species **1** in 62% yield. The intermediate (**1**) was slowly added to a large excess (more than 10 equiv) of 1,4-bis(2-thioxothiazolidin-1-yl)carbonyl-2,3-dimethoxybenzene or 1,3-bis(2-thioxothiazolidin-1-yl)carbonyl-2-methoxybenzene, to produce the ligands as monothiazolide, protected intermediates (**2** and **5**, respectively). Purification by silica gel flash chromatography gave the intermediates as yellow foams. These compounds are suitable for reacting with a wide variety of primary and some secondary amines. Reaction with aqueous methylamine (40 wt %) displaced the remaining thiazolide groups, and deprotection with an excess of BBr_3 in dry CH_2Cl_2 removed both the methyl and benzyl protecting groups to give the ligands (**4**, **7**) as the hydrobromide salts after aqueous workup.

The iron complexes were prepared by reacting a methanolic solution of the ligand with Fe^{3+}, followed by addition of base. The neutral Fe[TREN-Me-3,2-HOPOIAM] complex could be

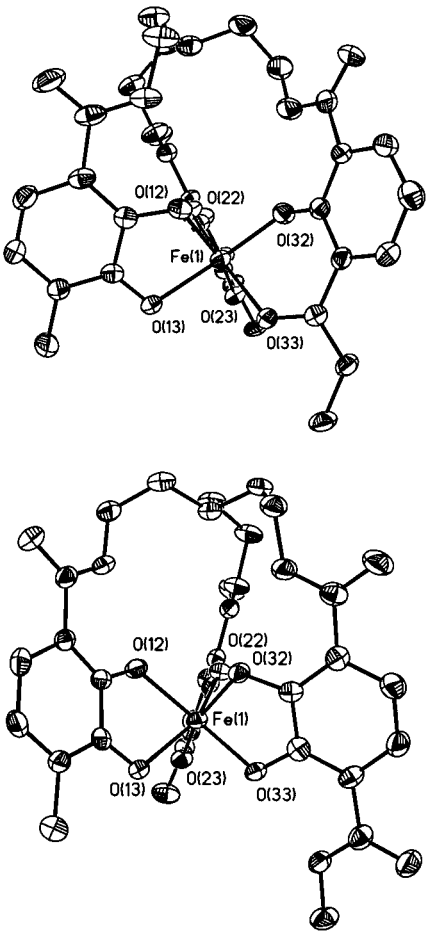


Figure 1. Structural representations (ORTEP, 50% probability ellipsoids) of Fe[TREN-Me-3,2-HOPOIAM] (top) and Fe[TREN-Me-3,2-HOPOTAM]$^-$ (bottom) with atom-numbering schemes given for the iron atom and immediate coordination sphere. Solvent, counterions, and hydrogens omitted for clarity.

purified by conventional flash silica column chromatography. Both complexes could be recrystallized from a variety of solvent systems. Single-crystal structural characterization of the complexes used crystals obtained from solvent diffusion methods. Figure 1 shows structural diagrams (ORTEP) of both complexes.

The reduction potentials of the ferric complexes were determined by square wave voltammetry at a HMDE. A set of voltammograms are illustrated for the Fe[TREN-Me-3,2-HOPOIAM] complex in Figure 2, upper panel. Reversibility of the voltammetric waves was verified by transforming the current−potential response according to eq 1 to give the function Γ, as plotted in Figure 2, lower panel. A high degree of linearity ($R^2 \geq 0.999$) for this function was observed within a potential window of 100 mV about the standard reduction potential ($E°$) for all frequencies (5−50 Hz). The value for $E°$ determined from this plot was in perfect agreement with the peak potential, E_p. This reversible response for the complexes was confined to a mildly alkaline pH region; at lower pH the $E°$ values were no longer constant and moved to more positive values with distortion of the waveform. At higher pH values the waveform also became distorted and the peak currents diminished as the solution became decolorized due to hydroxide competition for ferric iron. For the Fe[TREN-Me-3,2-HOPOIAM] system the standard reduction potential ($E°$) was determined as -226 ± 4 mV vs NHE (70 measurements, pH 7.5−9.5), and for the Fe[TREN-Me-3,2-HOPOTAM] system a value of -422 ± 8 mV vs NHE was obtained (63 measurements, pH 8.4−10.9).

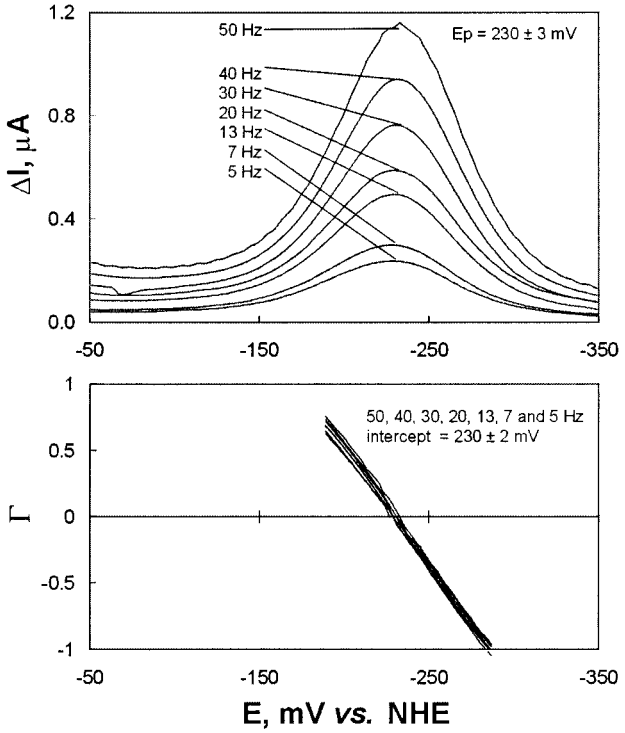


Figure 2. Upper panel: Square wave voltammograms at the HMDE of 5×10^{-5} M Fe[TREN-Me-3,2-HOPOIAM] in 0.01 M ammonium acetate buffer, pH 8.59, ionic strength 0.1 M (KCl), $E_{SW} = 25$ mV, $E_{step} = 2$ mV, frequencies given in hertz. Lower panel: Conversion of the voltammograms to the Γ function, according to eq 1.

The protonation and iron formation constants are listed in Table 2. The values were determined using potentiometric and spectrophotometric techniques. Competition methods were used to determine the ferric formation constants because iron is bound so strongly to the ligands that it is not liberated by acid until negative pH: addition of EDTA removes the metal at pH values less than 4 and allows the formation constants to be determined. Under the conditions of the titrations there is significant formation of both FeL and FeLH with at least 40% formation of each species (a species distribution diagram calculated for the conditions of the competition titrations is provided in Figure S1 of the Supporting Information).

Two methods were employed in the investigation of ferric formation constants. Incremental titrations have the advantages that they are easily automated, use materials more efficiently, and are less prone to solution handling errors. A practical limitation of incremental titrations is that the equilibration time is limited to 2 h or less. In contrast, the batch titrations used an equilibration time of at least 100 h. The results in Table 2 show good agreement between the incremental and batch titrations, indicating that both sets of data represent the equilibrium state.

Both types of competition titration were analyzed spectrophotometrically. A spectral data set from one of the competition titrations is illustrated in Figure S2 of the Supporting Information. These experiments exploit the broad ligand-to-metal charge-transfer (LMCT) bands which increase in intensity as iron exchanges from the colorless EDTA complex to the red Fe[heteropodand] complex. The quality of fit in the nonlinear least squares fit to the spectral data is illustrated in the Supporting Information. Both metal complexes are purple-red to red in color. The LMCT bands of Fe[TREN-Me-3,2-HOPOTAM]$^-$ are less well defined than those in Fe[TREN-Me-3,2-HOPOIAM] (vide infra). One of the visible transitions in Fe[TREN-Me-3,2-HOPOTAM]$^-$ is centered at 532 nm ($\epsilon =$

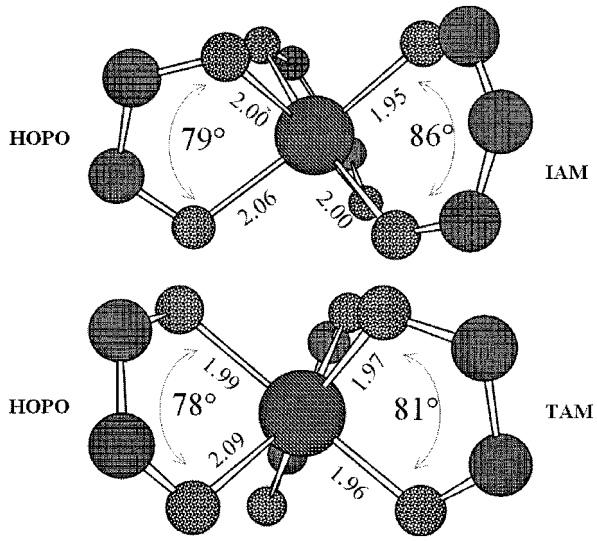


Figure 3. Asymmetric coordination environments of the iron cations in the complexes Fe[TREN-Me-3,2-HOPOIAM] (top) and Fe[TREN-Me-3,2-HOPOTAM]$^-$ (bottom) showing bond distances and angles. The labels "TAM", "IAM", and "HOPO" indicate the rings formed by each of the bidentate chelating units.

4600 M^{-1} cm^{-1}), and the other is located at about 426 nm (ϵ = 6100 M^{-1} cm^{-1}) and appears as a low-energy shoulder of a more intense $\pi \rightarrow \pi^*$ transition at 338 nm (ϵ = 14400 M^{-1} cm^{-1}). Fe[TREN-Me-3,2-HOPOIAM] displays one LMCT band at 436 nm (ϵ = 5900 M^{-1} cm^{-1}) and a second, less intense transition at 530 nm (ϵ = 4100 M^{-1} cm^{-1}). The bimodal nature of the LMCT bands is characteristic of HOPO complexes;[1,31] however, the two transitions are generally closer in intensity than is observed in this case. The significant increase in intensity of the higher energy band in Fe[TREN-Me-3,2-HOPOIAM] is likely due to the contribution of the 2-hydroxyisophthalamide chelate which possesses a LMCT band with iron at around 445 nm (in the tris-bidentate complex).[8] Fe[TREN-Me-3,2-HOPOIAM] also has a strong $\pi \rightarrow \pi^*$ transition in the UV region at 328 nm (ϵ = 18400 M^{-1} cm^{-1}).

Discussion

The Fe[TREN-Me-3,2-HOPOIAM] complex displays the anticipated coordination environment with both the hydroxypyridinonate and 2-hydroxyisophthalate moieties acting as bidentate chelators (Figure 1). The three phenolates participate in strong hydrogen bonds with adjacent amide protons of the scaffold. This important structural feature has been demonstrated in related ligands.[2,7,31−34] Close inspection of the metal center reveals an inhomogeneous coordination sphere created by the heteropodate ligand (Figure 3). The Fe−O distance for the 2-hydroxy oxygen of the hydroxypyridinonate chelators is 0.04 Å shorter than that of the 3-carbonyl oxygen, typical for this type of chelator.[2] In the 2-hydroxyisophthalamide ligand, the negatively charged 2-hydroxy oxygen is held 0.05 Å closer to the iron center than the ligating carbonyl oxygen.[8] Between chelators, the Fe−O bond length of the phenolate oxygen in the isophthalamide (1.95 Å) is 0.06 Å shorter than those of the HOPO units (2.00 and 2.02 Å). The Fe−O distance of the ligated carbonyl group in the isophthalamide chelator (2.00 Å) is also shorter than those of the HOPO groups (2.04 and 2.06 Å) by 0.05 Å. The average twist angle, defined by the angles between the two coordinating atoms of each chelate projected onto the plane perpendicular to the idealized 3-fold axis, is 39°.[35] This value is more distorted from octahedral geometry than the values for both analogous homopodands, Fe[TRENIAM] and Fe[TREN-Me-3,2-HOPO], which have twist angles of 50° and 42°, respectively.[8,36]

The TREN-Me-3,2-HOPOTAM ligand is hexadentate with two hydroxypyridinonate chelators and one 2,3-dihydroxyterephthalamide chelator saturating the coordination sphere of the ferric ion (Figure 1). The bidentate chelators benefit from a total of four stabilizing phenolate hydrogen bonds: one from each of the HOPO rings and two from the terephthalamide ring.[37] The negative charge of the complex is balanced by the presence of a potassium counterion, poised on the open face of the complex, away from the TREN scaffold. The potassium ion is seven coordinate, ligated by four water molecules, two HOPO ring carbonyl groups, and one HOPO amide oxygen. The metal center is again in an asymmetric coordination environment created by the different chelators of the ligand (Figure 3). As in Fe[TREN-Me-3,2-HOPOIAM], the oxygens of the HOPO chelators in Fe**[**TREN-Me-3,2-HOPOTAM]$^-$ bind the metal in an asymmetric fashion (average Fe−O bond lengths 1.99 and 2.09 Å, respectively). The dianionic 2,3-dihydroxyterephthalamide chelate is bound closely to the metal center with an average Fe−O bond length of 1.99 Å. The twist angle of the complex is 32°, also smaller than expected from the calculated and experimental values of the analogous symmetric complexes.[1,34,35]

The formation constants (Table 2) are greater for the TREN-Me-3,2-HOPOTAM ligand; however, this ligand is also more basic (greater K^a values) and hence the Fe[TREN-Me-3,2-HOPOTAM]$^-$ complex is more sensitive to proton competition at low pH values. At pH 7.4 the TREN-Me-3,2-HOPOTAM ligand displays a pM value 3.5 units higher than that for the TREN-Me-3,2-HOPOIAM ligand (Table 2). For both ligands the pM values are high and comparable with many siderophores; e.g., enterobactin, desferrioxamine, and alcaligin have pM values of 35.5, 26.6, and 23.0, respectively.[38−41] Both ferric heteropodand complexes exhibit a single protonation reaction (speciation diagrams are provided in Figure S3 of the Supporting Information), the constant for which was essentially identical for the two systems ($\log K^a = \log \beta_{111} - \log \beta_{110} = 4.27$ for Fe[TREN-Me-3,2-HOPOIAM], 4.56 for Fe[TREN-Me-3,2-HOPOTAM]$^-$). The reaction corresponds to protonation of the capping tertiary amine of the TREN scaffold. This group is far less basic than is observed in tertiary alkylamines (e.g., $\log K^a$ = 9.4 for trimethylamine[42] and 10.7 for triethylamine[43]) due to hydrogen-bonding interactions with the three amide protons of the scaffold.

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This has been confirmed by the synthesis of a monoprotic derivative of TREN in which all primary amines were converted to amides.[12]

Substitution into the ligand structure of the 2,3-dihydroxyterephalamide chelator for the isophthalamide unit results in a negative shift of the redox potential by 196 mV (3.3 × 59 mV), indicating an induced selectivity for the ferric redox state by greater than 3 orders of magnitude. This is consistent with the behavior of 2,3-dihydroxyterephthalamide ligands which are known to be extremely powerful Fe^{3+} chelators and to stabilize this oxidation state of the metal.[44,45]

The formation constants and reduction potentials for the ferric heteropodand complexes relative to the standard Fe(III/II)-couple[46] allow the ferrous formation constants to be calculated using standard thermodynamic relationships.[47,48] The resulting ferrous stability constants are given in Table 2.

Speciation calculations indicate that the ferrous complexes begin to dissociate to give free Fe^{2+} and ligand from below pH 6 and pH 6.5 for Fe[TREN-Me-3,2-HOPOIAM]$^-$ and Fe[TREN-Me-3,2-HOPOTAM]$^{2-}$, respectively. The upper limit for reversible electrochemistry is well predicted by the point at which ferric iron is removed from the complexes as FeO(OH)(s): pH 9.8 and pH 11.5 for Fe[TREN-Me-3,2-HOPOIAM] and Fe[TREN-Me-3,2-HOPOTAM]$^-$, respectively.[30]

Conclusion

A parent ligand based on 3,2-hydroxypyridinonate (HOPO) chelates has been modified by a single substitution with either a 2-hydroxyisophthalamide or 2,3-dihydroxyterephthalamide unit in order to vary systematically the ligand properties. One of the resulting ligands (TREN-Me-3,2-HOPOIAM) retains the high affinity for ferric iron, but is relatively easy to reduce to the ferrous state. In the second ligand (TREN-Me-3,2-HOPOTAM) the selectivity for ferric iron has been increased and the resulting chelate is stable within a higher region of pH. Structural characterization has demonstrated the expected hexacoordinate binding of the metal center by both ligands. The inhomogeneous ligand environment of the heteropodands leads to a coordination sphere about the metal center having a lower twist angle than any of the homogeneous parent complexes. Finally, the 2-hydroxyisophthalate and 2,3-dihydroxyterephthalate chelating units are easily derivatized through the pendant carboxyl groups. Such variability is desirable for optimization of practical applications of such ligands and is an important characteristic, given the promise shown by the parent ligand in applications such as metal decorporation[1,3] and as a potential MRI contrast agent.[2,6]

Acknowledgment. We thank Dr. Fred Hollander for assistance with the X-ray structure determinations and Dr. Jide Xu and Dr. Christopher J. Sunderland for helpful discussions. This work was supported by the National Institutes of Health (NIH Grant DK32999).

Supporting Information Available: CIF format files for both X-ray crystallographic structures. A species distribution diagram showing the relative fractions of iron-containing species as a function of pH, calculated for the conditions of one of the competition titrations (Fe/TREN-Me-3,2-HOPOTAM/EDTA), and a figure showing the observed and calculated spectral changes for the same titration. A speciation diagram for each of the ligand systems as a function of pH. A table of the values used for the constants incorporated as fixed parameters in the refinements. This material is available free of charge via the Internet at http://pubs.acs.org.

IC000239G

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